Pharmacological Augmentation of NMDA Receptor Function for Treatment of Schizophrenia[a]

ILANA ZYLBERMAN,[b,d] DANIEL C. JAVITT,[b-d] AND STEPHEN R. ZUKIN[b-e]

Departments of [b]Psychiatry and [c]Neuroscience
Albert Einstein College of Medicine of Yeshiva University
Bronx, New York 10461

[d]Bronx Psychiatric Center
Bronx, New York

Acute low-dose administration of phencyclidine (1,1-phenylcyclohexylpiperidine; PCP) induces a schizophrenia-like psychotic state in nonpsychotic subjects. By contrast to amphetamine administration, PCP psychosis incorporates negative symptoms (withdrawal, negativism, autism) and cognitive dysfunction (impairment of abstract thinking, symbolic thinking, attention, and perception), as well as positive symptoms closely resembling those in schizophrenia.[1-8] Neuropsychological tests requiring sustained attention and paired-associate learning are most affected by low-dose PCP administration,[1] suggesting that, as in schizophrenia,[9,10] prefrontal and temporohippocampal processing may be most severely disturbed by PCP. Furthermore, subjects with schizophrenia are uniquely sensitive to the psychotomimetic effects of PCP. A single dose of PCP administered to recompensated schizophrenic subjects recreated the presenting symptomatology for days[3] to weeks[2,5] without inducing symptoms and signs atypical of schizophrenia; by contrast, psychotomimetic PCP effects in normal subjects typically resolve within four to six hours, although a minority of subjects—approximately 20%—may develop symptoms for a longer period of time. Subjects predisposed to schizophrenia based upon premorbid symptoms or family history appear to be at increased risk for developing prolonged symptoms.[11] Nonschizophrenic patients with PCP psychosis are difficult to differentiate from acute schizophrenics on the basis of presenting symptomatology alone.[11,12] Administration of PCP to monkeys can simulate the abnormalities in event-related potentials seen in schizophrenic subjects.[13,14] Finally, patterns of brain metabolism determined by positron emission tomography in nonschizophrenic chronic PCP users have been reported to be abnormal and to resemble patterns seen in chronic schizophrenics.[15]

At serum concentrations (10–100 nM) calculated[16] to result from the selectively psychotomimetic human dose of 0.1 mg/kg of PCP, the only significant central nervous system (CNS) target site is the PCP receptor, which has a nanomolar affinity for PCP and binds PCP-like drugs with affinities paralleling their potencies in

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[e]Address correspondence to Stephen R. Zukin, M.D., Department of Psychiatry, Albert Einstein College of Medicine, 1300 Morris Park Avenue, F111, Bronx, NY 10461.

evoking PCP-specific behaviors (reviewed in ref. 17). The location of the PCP receptor within the interior of the ion channel gated by the *N*-methyl-D-aspartate (NMDA) receptor dictates that binding of PCP receptor ligands blocks NMDA receptor-mediated ion flux in a fashion that cannot be surmounted by increasing agonist (L-glutamate) concentration.

The association of PCP-induced blockade of NMDA receptor channels with induction of a schizophrenia-like psychosis in normal subjects and with long-lasting exacerbation of illness in previously stabilized schizophrenic patients suggests that an endogenous deficiency of NMDA receptor-mediated neurotransmission may play a role in schizophrenia (reviewed in ref. 17).

A particularly intriguing question is whether neuroleptic-resistant schizophrenia with prominent negative and cognitive symptoms may benefit from pharmacological augmentation of NMDA receptor-mediated neurotransmission. Of the multiple regulatory sites of the NMDA receptor (reviewed in ref. 17), the glycine site is the most logical candidate for pharmacological augmentation of NMDA receptor activation. The NMDA receptor is activated according to a multistate system in which sequential binding of two molecules of the agonist L-glutamate is required to attain a conformation from which activation can take place.[18] Once this prerequisite has occurred, the equilibrium between the activated and the resting conformations is regulated by the local concentration of glycine. Glycine acts at a specific strychnine-insensitive binding site on the NMDA receptor complex.[19] If glycine is absent, NMDA receptor activation is not observed.[20]

No high-affinity transport of glycine occurs across the blood-brain barrier, so that under normal circumstances peripheral glycine contributes little to CNS glycine levels.[21] However, pharmacological doses of glycine have been shown to increase CNS glycine levels in rodents.[22,23] Glycine is without significant side effects at doses up to 3 g/kg,[24] and has been employed in doses as high as 60 g per day without significant toxicity.[25]

In addition to increasing brain glycine levels, orally administered glycine has been shown to reverse PCP-induced behaviors in rodents,[23] suggesting that the increased brain glycine level leads to potentiation of NMDA receptor-mediated neurotransmission. Furthermore, a high-affinity glycine reuptake mechanism has recently been described, suggesting a physiological mechanism for regulation of synaptic glycine concentration at the NMDA receptor.[26]

Previous studies of glycine therapy in schizophrenia have yielded conflicting results, possibly because of variations in dosage, patient population, and rating instruments.[27–30] In a study conducted at Bronx Psychiatric Center,[31] we used a dose of glycine higher than that used in any previous trial, and employed a rating instrument designed to discriminate negative symptoms from positive symptoms and general psychopathology. Fourteen male subjects meeting DSM-III-R[32] criteria for schizophrenia were maintained on clinically determined optimal doses of neuroleptic drug and randomly assigned to receive either glycine or placebo. Glycine therapy was titrated upward to a maximum dose of 0.4 g/kg body weight (approximately 30 g per day) during the first two weeks of an 8-week treatment period. After completion of the double-blind phase, all patients were offered open-label glycine continuation for an additional 8-week period. One additional subject was treated with open-label glycine only. Subjects were rated with the Positive and Negative Syndrome Scale (PANSS),[33] the Extrapyramidal Rating Scale,[34] and the Abnormal Involuntary Movement Scale (AIMS).[35] Statistical analyses (two-tailed) were accomplished using the SPSS/PC + computer program. Values represent mean ± standard deviation.

There were no between-group differences in age (glycine, 36.0 ± 9.7 yr; placebo, 38.1 ± 7.2 yr), duration of illness (glycine, 15.5 ± 8.1; placebo, 20.0 ± 6.6 yr) or

dosage of neuroleptic drug (glycine, 1450 ± 826; placebo, 1194 ± 658 chlorpromazine equivalents per day). No between-group differences were found in baseline ratings of negative symptoms (glycine, 21.5 ± 8.6; placebo, 24.6 ± 5.3), positive symptoms (glycine, 23.5 ± 5.6; placebo, 22.2 ± 4.7) or general psychopathology (glycine, 40.7 ± 7.9; placebo, 45.0 ± 8.3). A decrease in negative symptoms was observed in all subjects who received glycine during the double-blind phase, but in only 2 of 7 subjects who were given placebo (Fisher exact test $p < 0.025$). Subjects in the glycine group showed a mean percentage improvement of 15.3 ± 7.7% as compared to 1.4 ± 7.7% in the placebo-treated group ($t = 5.28$, $p < 0.002$). Repeated measures ANOVA with baseline as covariate across the 8-week study period demonstrated significant effects of glycine ($F_{1,11} = 11.74$, $p = 0.006$) and time ($F_{1,8} = 8.11$, $p = 0.022$) and also a significant glycine-by-time interaction ($F_{1,8} = 8.34$, $p = 0.02$). Subjects who received glycine during the double-blind phase did not show further significant change in negative symptom ratings during the subsequent open-label extension. By contrast, subjects who received placebo during the double-blind phase showed a 19.6 ± 10.0% ($t = 5.19$, $p < 0.002$) improvement in negative symptoms. Pooling of results across double-blind and open-label phases indicated a highly significant 17.1 ± 8.6% improvement in negative symptom ratings at week 8 of glycine treatment ($t = 6.84$, $p < 0.0001$). Glycine treatment had no significant effects on ratings of positive symptoms (change scores 0.9 ± 5.2 and 0.8 ± 6.0 for the glycine- and placebo-treatment groups, respectively), general psychopathology (change scores 3.3 ± 5.1 and 2.9 ± 6.9, respectively), or on EPS or tardive dyskinesia parameters. Pre- minus posttreatment EPS change scores for the glycine and placebo groups, 1.0 ± 3.1 and 4.0 ± 8.7, did not differ from each other or from zero. AIMS ratings were zero to minimal in both glycine and placebo groups before and after treatment. Glycine treatment was not associated with changes in serum chemistry or hematological values. One subject, while receiving double-blind glycine, reported lower-extremity weakness that ceased after temporary dose reduction and did not recur following resumption of the full dose.

The relatively modest magnitude of the glycine effect observed in this study may stem from the fact that peripherally administrated glycine gains entry to the CNS only via passive diffusion across the blood-brain barrier. It is possible that higher doses of glycine may be required to produce more robust effects. Other agents that have been evaluated for treatment of neuroleptic-resistant negative symptoms, including anticholinergics[36] and dopamine agonists,[37] may also exacerbate positive symptoms. It is therefore noteworthy that the glycine-induced reduction in negative symptoms was not accompanied by an increase in positive symptoms. The failure of glycine to improve positive symptoms in this study may result from the fact that all subjects were receiving high doses of neuroleptic drugs. We showed that in mice, peripheral administration of haloperidol (0.5 mg/kg) 30 min after peripheral pretreatment with glycine (0.4 g/kg) or saline resulted in statistically indistinguishable brain haloperidol levels in the glycine- and saline-pretreated groups,[31] suggesting that the glycine-induced decrease in negative symptoms observed in our clinical study was not due to a glycine-induced change in the effective dosage of the neuroleptic drug. The lack of glycine-induced change in EPS scores indicates that the glycine-induced reduction in negative symptoms did not result from a reduction in neuroleptic-induced extrapyramidal symptoms.

These results provide additional support for the hypothesis that impaired NMDA receptor-mediated neurotransmission may underlie symptoms of schizophrenia that respond incompletely or not at all to treatment with neuroleptic agents, and suggest that emerging knowledge of NMDA receptor regulation should be exploited to

develop increasingly effective pharmacological strategies for augmentation of NMDA receptor function.

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